

⑫

**EUROPEAN PATENT APPLICATION**

⑰ Application number: 86309815.8

⑤① Int. Cl.⁴: **C 07 D 333/34, A 61 K 31/38**

⑱ Date of filing: 16.12.86

③① Priority: 24.12.85 US 813318

⑦① Applicant: **MERCK & CO. INC., 126, East Lincoln Avenue  
P.O. Box 2000, Rahway New Jersey 07065 (US)**

④③ Date of publication of application: 08.07.87  
Bulletin 87/28

⑦② Inventor: **Baldwin, John J., 621 Gypsy Hill Circle,  
Gwynedd Valley Pennsylvania 19437 (US)**  
Inventor: **Habecker, Charles N., 361 Oakland Avenue,  
Lansdale Pennsylvania 19446 (US)**  
Inventor: **Ponticello, Gerald S., 2045 Spring Valley Road,  
Lansdale Pennsylvania 19446 (US)**

⑧④ Designated Contracting States: CH DE FR GB IT LI NL

⑦④ Representative: **Hesketh, Alan, Dr., European Patent  
Department Merck & Co., Inc. Terlings Park Eastwick  
Road, Harlow Essex, CM20 2QR (GB)**

⑥④ **Substituted thiophene-2-sulfonamide antiglaucoma agents.**

⑥⑦ Thiophene-2-sulfonamides with an alkyl or substituted-alkyl and an alkyl-S(O)<sub>n</sub>-substituent are carbonic anhydrase inhibitors useful in the treatment of elevated intraocular pressure.

2151S/0245A

- 1 -

17324

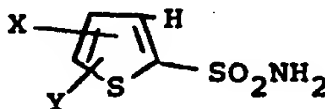
TITLE OF THE INVENTION

SUBSTITUTED THIOPHENE-2-SULFONAMIDE ANTIGLAUCOMA  
AGENTS

SUMMARY OF THE INVENTION

5           This invention relates to novel  
thiophene-2-sulfonamides useful in the treatment of  
elevated intraocular pressure. More particularly  
this invention relates to compounds having the  
structural formula:

10



15

wherein X and Y are hereinafter defined, as well as  
the pharmaceutically and ophthalmologically  
acceptable salts thereof. This invention also  
relates to pharmaceutical compositions and the use  
20 thereof for systemic and ophthalmic use employing a

novel compound of this invention as active ingredient for the treatment of elevated intraocular pressure, especially when accompanied by pathological damage such as in the disease known as glaucoma.

5

#### BACKGROUND OF THE INVENTION

Glaucoma is an ocular disorder associated with elevated intraocular pressures which are too high for normal function and may result in  
10 irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects,  
15 is now believed by many ophthalmologists to represent the earliest phase of glaucoma.

Many of the drugs formerly used to treat glaucoma proved not entirely satisfactory. Indeed, few advances were made in the treatment of glaucoma  
20 since pilocarpine and physostigmine were introduced. Only recently have clinicians noted that many  $\beta$ -adrenergic blocking agents are effective in reducing intraocular pressure. While many of these agents are effective in reducing intraocular pressure,  
25 they also have other characteristics, e.g. membrane stabilizing activity, that render them unacceptable for chronic ocular use. (S)-1-~~text~~-Butylamino-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol, a  $\beta$ -adrenergic blocking agent, was found to reduce  
30 intraocular pressure and to be devoid of many unwanted side effects associated with pilocarpine and, in addition, to possess advantages over many other  $\beta$ -adrenergic blocking agents, e.g. to be devoid

of local anesthetic properties, to have a long duration of activity, and to display minimal tolerance.

5        Although pilocarpine, physostigmine and the  $\beta$ -blocking agents mentioned above reduce intraocular pressure, none of these drugs manifests its action by inhibiting the enzyme carbonic anhydrase and, thereby, impeding the contribution to aqueous humor formation made by the carbonic anhydrase pathway.

10       Agents referred to as carbonic anhydrase inhibitors, block or impede this inflow pathway by inhibiting the enzyme, carbonic anhydrase. While such carbonic anhydrase inhibitors are now used to treat intraocular pressure by oral, intravenous or  
15       other systemic routes, they thereby have the distinct disadvantage of inhibiting carbonic anhydrase throughout the entire body. Such a gross disruption of a basic enzyme system is justified only during an acute attack of alarmingly elevated intraocular  
20       pressure, or when no other agent is effective. Despite the desirability of directing the carbonic anhydrase inhibitor only to the desired ophthalmic target tissue, no topically effective carbonic anhydrase inhibitors are available for clinical use.

25       However, topically effective carbonic anhydrase inhibitors are reported in U.S. Patents 4,386,098; 4,416,890; and 4,426,388. The compounds reported therein are 5 (and 6)-hydroxy-2-benzo-thiazolesulfonamides and acyl esters thereof.

30       To be an effective and acceptable topical agent, an ophthalmic carbonic anhydrase inhibitor must not only penetrate the ophthalmic tissues to reach the active sites within the eye, but it must

2151S/0245A

- 4 -

17324

also be devoid of those side effects including irritation, allergic reaction and the like which would militate against long term administration.

## 5 DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention have structural formula:



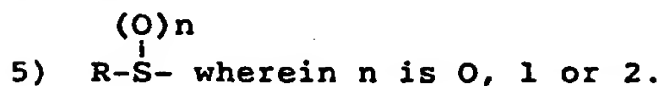
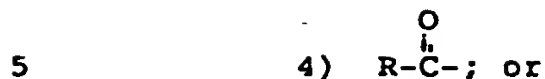
wherein:

- 15 X is
- 1) -CN,
  - 2) halo such chloro, bromo or fluoro,
  - 3) R wherein R is C<sub>1-5</sub> alkyl, either straight or branched chain and either unsubstituted or substituted with one or more of:
    - 20 i) -OH
    - ii)  $\begin{array}{c} \text{R}^1 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}^2 \end{array}$  wherein R<sup>1</sup> and R<sup>2</sup> are
 

25 independently hydrogen, C<sub>1-5</sub> alkyl, or C<sub>2-5</sub> alkanoyl,
    - iii) aryl, such as phenyl or naphthyl, either unsubstituted or substituted with one or more of
 

30 -OH or C<sub>1-3</sub> alkyl, or

- iv) a 6-membered nitrogen containing heteroaryl such as pyridyl, pyrazinyl, or pyrimidinyl;



- Y is            1)  $\text{C}_{1-5}$  alkyl, either straight chain, branched chain or cyclic, and either unsubstituted or substituted with
- 10                    a) hydroxy,  
                      b)  $\text{C}_{1-3}$  alkoxy,  
                      c) methoxyethoxymethoxy,  
15                    d) amino,  
                      e) mono- or di- $(\text{C}_{1-5}$  alkyl)amino,  
                      f)  $\text{C}_{2-5}$  alkanoylamino;  
                      g) aryl, such as phenyl or naphthyl, either unsubstituted or
- 20                    substituted with one or more of -OH or  $\text{C}_{1-3}$  alkyl, or  
                      h) a 6-membered nitrogen containing heteroaryl such as pyridyl, pyrazinyl, or pyrimidinyl;
- 25                    2)  $-\overset{\text{O}}{\underset{\text{I}}{\text{S}}}-(\text{C}_{1-5} \text{ alkyl})$ , wherein the alkyl is  
                      either straight or branched or cyclic and either unsubstituted or substituted with items a) through h) as defined
- 30                    above;
- 3) halo such as chloro, fluoro or bromo;  
with the proviso that X and Y are not both halo.

2151S/0245A

- 6 -

17324

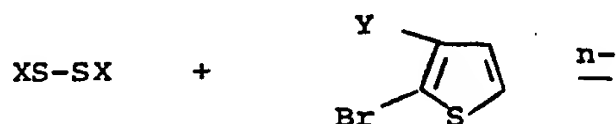
(O)<sub>n</sub>

It is preferred that X is R-S- and that it be a 5-substituent. It is further preferred that R and Y are independently C<sub>1-5</sub> alkyl or substituted C<sub>1-5</sub> alkyl.

It is even more preferred that R is C<sub>1-5</sub> alkyl, hydroxy-C<sub>1-5</sub> alkyl, or mono- or di-(C<sub>1-5</sub> alkyl)amino-C<sub>1-5</sub> alkyl, and that n is 0 or 2.

A novel process for preparing sulfides of this invention comprises treating a bromothiophene with an organometallic such as n-butyl lithium at about -70°C in an ethereal solvent such as ether, THF, glyme or the like for about 1 to 5 hours. This mixture is then added to a dialkyldisulfide in an inert atmosphere in an ethereal solvent at about -25 to -5°C. After about 15 minutes to 2 hours the mixture is then refluxed for about 1 to 4 hours. The reaction scheme is as shown below:

20



Functional groups on Y such as hydroxyl must be protected during the reaction for example as the methoxyethoxymethyl ether, which is readily removed after the reaction with a dilute mineral acid such as sulfuric acid at about 15 to 30°C for about 0.5 to 3 hours.

The 4-alkylthio-5-substituted alkylthiophene-2-sulfonamides are prepared from known 3-alkylthiothiophene-2-carboxaldehyde. Treatment of the

2151S/0245A

- 7 -

17324

aldehyde with a Grignard reagent, LAH or the like yields the corresponding alcohol derivatives.

Protection of the alcohol as the MEM ether or any other suitable protecting group such as THP,

5 tert-butyldimethylsilyl or the like followed by the incorporation of the 2-sulfonamide group by chemistry described below provides the desired 4-alkylthio-5-substituted alkylthiophene-2-sulfonamides.

10 The 2-thio compounds may also be prepared by treating a 2-bromothiophene with a cuprous hydroxy-alkyl mercaptide in refluxing quinoline for about 3-6 hours.

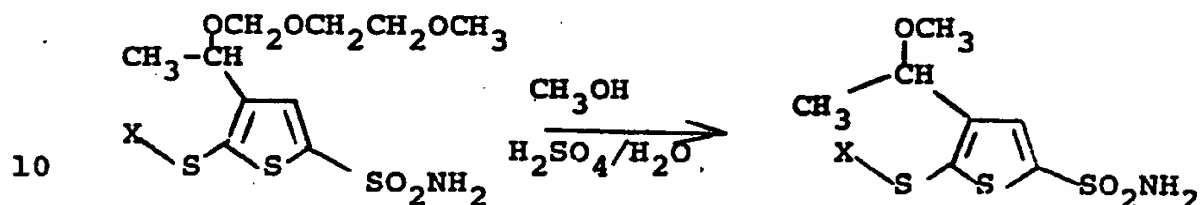
The methoxyethoxymethyl group may also be removed by treating the ether with dimethylboron  
15 bromide in chlorinated alkane such as methylene chloride at about  $-78^{\circ}\text{C}$  for about 0.5 to 2 hours.

A novel process for preparing the sulfones of this invention comprises treating the sulfide with an oxidizing agent such as OXONE<sup>R</sup> ( $2\text{KHSO}_5 \cdot \text{K}_2\text{SO}_4 \cdot \text{KHSO}_4$ )  
20 (Dupont) followed by removal of any protecting group. It is often advisable to protect hydroxyl groups during the oxidation and it is readily accomplished by means of methoxyethoxymethyl ethers which can be removed by treatment with a mineral acid as described  
25 previously. The oxidation proceeds readily in aqueous alcohol at about 15 to  $30^{\circ}\text{C}$  over a period of about 4 hours.

The novel sulfoxides of this invention are prepared by oxidation of the sulfides with sodium  
30 metaperiodate at about 15 to  $25^{\circ}\text{C}$  in aqueous alcohol for about 8 to 36 hours.



Those compounds wherein the Y group carries an alkoxy group are prepared by treating the methoxyethoxymethyl ether in the appropriate alcohol with cold 50% (v/v) aqueous sulfuric acid for about 15 minutes to 1 hour at ambient temperature. The reaction is exemplified by the following:



The sulfonamide group is introduced to the 2-position of the thiophene by treating the thiophene with an organometallic reagent such as n-butyl lithium in an ethereal solvent such as THF at  $-78^\circ\text{C}$  for about 1-3 hours. The lithium thiophene solution is then exposed to sulfur dioxide gas for about 2 to 5 hours while warming to about  $-40^\circ\text{C}$ . The isolated lithium salt is then dissolved in sodium bicarbonate solution and treated with N-chlorosuccinimide. The resulting thiophene sulfonyl chloride in an inert solvent such as acetone is then added to concentrated ammonium hydroxide dropwise at about ice-bath temperature and the mixture is aged for about 0.5 to 2 hours.

Novel compounds wherein the Y group carries an amino substituent are prepared by treating the corresponding hydroxyl compound with sulfuric acid in an excess of acetonitrile at about  $15$  to  $25^\circ\text{C}$  for about 18 to 36 hours (Ritter Reaction). The resulting acetamino compound may be reduced with borane dimethylsulfide complex in an ethereal solvent at reflux temperature for about 0.5 to 3 hours.

Alternatively, the monoalkylamino derivative may be prepared by acid hydrolysis of the intermediate amide derived from the Ritter reaction followed by re-acylation with an alkanoyl chloride or anhydride to provide a new amide. Reduction of this amide with borane as described above yields the monoalkylamino derivative. The corresponding dialkylamino derivatives are prepared from the corresponding monoalkylamino derivative by acylation with an alkanoyl chloride or anhydride followed by reduction of the amide with diborane to provide the dialkylamino derivatives.

A process of preparing ketones as exemplified by **8** ( $Y = -CH_3$ ,  $-CH_2OH$ ,  $-CH(CH_3)OH$ ) of the invention is described in Scheme I. Functional groups on **Y** such as hydroxy must be protected during the reaction sequence for example as the methoxyethoxymethyl ether. Bromination of **1** with NBS/ $CCl_4$  provides the 2 bromothiophene **2**. Treatment of **2** with n-butyl lithium followed by reaction with either dimethylformamide or dimethylacetamide yields the formyl or acetyl derivative **3**, respectively. Reduction of **3** with chemical reducing agents such as  $LiAlH_4$ ,  $NaBH_4$  or the like yields the alcohol **4**. In order to differentiate alcohols when another protected hydroxyl is present, the second alcohol moiety is protected as the tert-butyldimethylsilyl ether **5**. Using previously described chemistry the sulfonamide group is next incorporated onto **5** to yield **6**. The silyl group is removed by the use of  $F^-$  to provide **7** and the alcohol **7** is oxidized by either  $MnO_2$ ,

Sarrett oxidation, a Jones oxidation, or the like to the ketone 8. In the examples where Y contains a hydroxyl group protected as a methoxyethoxymethyl ether, the group is removed by treatment with aqueous methanolic mineral acid. In cases where Y contains an amino group these compounds are prepared from the alcohol as previously described above (Ritter reaction).

5-Aralkylsulfone-4-alkylketonethiophene-2-sulfonamides are prepared from 2,3-dibromothiophene. Treatment with n-BuLi, LDA or the like provides the 2-lithiothiophene which is then treated with an aralkyldisulfide to provide the 2-aralkylsulfide-3-bromothiophene. Treatment with another equivalent of base, described above, yields the 3-lithio derivative which on reaction with DMF provides the 3-carboxaldehyde derivative. Manipulation of this structure as previously described provides the desired 5-aralkylsulfone-4-alkylketonethiophene-2-sulfonamides. By changing the order of reagents the corresponding 4-aralkylsulfone-5-alkylketonethiophene-2-sulfonamides may be prepared.

25

30



Those compounds wherein the X-group is -CN, are prepared from intermediate 2 (Scheme I).

Treatment of aldehyde 3 with hydroxylamine yields the syn- and anti-oximes 9. Dehydration of 9 with acetic anhydride, thionyl chloride, DMF, trifluoroacetic-  
5 anhydride or the like provides the nitrile 10. Treatment of 10 with lithium (diisopropyl)amide (LDA) followed by SO<sub>2</sub> and hydroxylamine-O-sulfonic acid yields the sulfonamide 11. Examples of Y containing  
10 hydroxyl and amino functions are prepared as previously described

Treatment of 2 with LDA followed by SO<sub>2</sub> and hydroxylamine-O-sulfonic acid gives the corresponding 2-sulfonamide-5-bromothiophene  
15 derivative.

The novel pharmaceutical formulations of this invention include formulations for systemic administration and ophthalmic formulations designed for topical ocular administration, preferably the latter.

20 The formulations for systemic administration comprise a non-toxic pharmaceutically acceptable carrier and an effective amount of one or more of the novel compounds of this invention. They may be in a form (a) for oral administration; e.g., as tablets, in  
25 combination with other compounding ingredients customarily used such as talc, vegetable oils, polyols, benzyl alcohols, gums, gelatin, starches and other carriers; dissolved or dispersed or emulsified in a suitable liquid carrier; in hard or soft capsules,  
30 encapsulated in a suitable material; or (b) for parenteral administration; e.g., dissolved or dispersed in a suitable liquid carrier as a solution, suspension or emulsion, or (c) for transdermal application, e.g. as a patch.

The active drugs of this invention are most suitably administered in the form of ophthalmic pharmaceutical compositions adapted for topical administration to the eye such as a solution, suspension, gel, ointment, or as a solid insert. Formulations of these compounds may contain from 0.01 to 15% and especially 0.5% to 2% of medicament. They may contain a novel compound of this invention as the sole medicament or may contain as well an effective amount of a  $\beta$ -adrenergic blocking agent such as timolol maleate or a parasympathomimetic agent such as pilocarpine. The two active principles are present in approximately equal amounts on a weight basis.

The pharmaceutical preparation which contains the active compound may be conveniently admixed with a non-toxic pharmaceutical inorganic or organic carrier. Typical of pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious

in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients  
5 such as sorbitan monolaurate, triethanolamine, polyoxyethylene sorbitan monopalmitate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like. Additionally, suitable ophthalmic vehicles can be  
10 used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like.

15 The pharmaceutical preparation may also be in the form of a solid insert such as one which after dispensing the drug remains essentially intact, or a bio-erodible insert that either is soluble in lacrimal fluids, or otherwise disintegrates.

20 Generally, doses of the present compounds of about 0.01 to about 50 mg/kg and preferably from about 0.1 to about 20 mg/kg of body weight per day may be used. Dosage may be single or multiple depending on the daily total required and the unit  
25 dosage.

#### EXAMPLE 1

4-(1-Hydroxypropyl)-5-methylsulfonylthiophene-2-sulfonamide

30 Step A: Preparation of 3-(1-Hydroxypropyl)-2-methylthiothiophene

To a stirred solution of ethylmagnesium bromide (60 ml, 0.12 mol of a 2.0M solution in THF)

in ether (50 ml) was added dropwise under a nitrogen atmosphere 2-methylthiophene-3-carboxaldehyde (15.8 g, 0.10 mol) in ether (10 ml) over a 1/2 hour period at ice bath temperature. The mixture was stirred at room temperature for 2 hours. The mixture was cooled in an ice bath and the complexes were decomposed by adding  $\text{NH}_4\text{Cl}$  (10.6 g) in 100 ml of water. The aqueous layer was separated and was extracted with ether (2 x 50 ml). These extracts were combined with the ether layer and were washed with saturated  $\text{NaCl}$  solution, saturated  $\text{NaHCO}_3$  solution and again with saturated  $\text{NaCl}$  solution. The ether solution was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo at room temperature to give 17.7 g of amber liquid (94%). TLC showed only minor impurities and NMR confirmed the structure.

Step B: Preparation of 3-[1-(Methoxyethoxymethoxy)-propyl]-2-methylthiophene

To a stirred solution of 3-(1-hydroxypropyl)-2-methylthiophene (17.7 g, 0.094 mol) in dry methylene chloride (100 ml) was added methoxyethoxymethyl chloride (20.6 g, 0.165 mol) followed by N,N-diisopropylethylamine (21.3 g, 0.165 mol). The mixture was stirred at room temperature overnight. The mixture was washed with water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo at room temperature to give 24.4 g of amber oil (94% yield). NMR confirmed the structure and mass spectral analysis confirmed the molecular weight at 276.09.



Step C: Preparation of 4-[1-(Methoxyethoxymethoxy)-propyl]-5-methylthiophene-2-sulfonamide

To a stirred solution of 3-[1-(methoxyethoxy-methoxy)propyl]-2-methylthiophene (24.0, 0.087  
5 mol) in dry THF (175 ml) cooled to  $-78^{\circ}\text{C}$  was added dropwise under nitrogen atmosphere n-butyl lithium (59.4 ml, 0.095 mol of a 1.6M hexane solution). The resulting deep red solution was stirred at about  $-70^{\circ}\text{C}$  for 2 hours and then  $\text{SO}_2$  gas was introduced  
10 over the surface of the solution at  $-70$  to  $-40^{\circ}\text{C}$  for 1 hour. The solution was stirred at about  $-40^{\circ}\text{C}$  for an additional 2 hours and was concentrated in vacuo to a viscous amber oil. The lithium salt was taken up in saturated  $\text{NaHCO}_3$  solution (175 ml) and was  
15 stirred at ice bath temperature as N-chlorosuccinimide (17.7 g, 0.13 mol) was added portionwise over 1/2 hour. The mixture was stirred at ice bath temperature for 2 hours and then was extracted with chloroform (3 x 70 ml). The combined extracts were  
20 washed with water, dried, filtered and concentrated in vacuo to an amber liquid. The resulting sulfonyl chloride was taken up in acetone (50 ml) and was added dropwise to concentrated  $\text{NH}_4\text{OH}$  (100 ml) at ice bath temperature over 1/2 hour. The mixture was  
25 stirred for an additional hour at that temperature and the acetone was removed in vacuo. The oil which separated was extracted into ether (3 x 50 ml), washed with water and re-extracted with 0.5N KOH solution (3 x 100 ml). The combined KOH extracts  
30 were washed with ether, acidified with 6N HCl and again extracted into ether (2 x 100 ml). The combined ether extracts were washed with saturated solutions of NaCl and  $\text{NaHCO}_3$  and again with

2151S/0245A

- 17 -

17324

saturated NaCl, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo at room temperature to give 24.3 g of amber liquid which was analytically pure (79%). NMR confirmed the structure and a molecular ion of M/Z 355 was observed in the mass spectrum.

Step D: Preparation of 4-[1-(Methoxyethoxymethoxy)propyl]-5-methylsulfonylthiophene-2-sulfonamide

The 4-[1-(methoxyethoxymethoxy)propyl]-5-methylthiophene-2-sulfonamide (7.1 g, 0.02 mol) was dissolved in 50/50 ethanol/water (60 ml). To the stirred solution was added OXONE<sup>R</sup> (18.4 g, 0.03 mol) and the mixture was stirred at room temperature for 4 hours. The acidic mixture was made slightly basic with sodium bicarbonate and the mixture was concentrated in vacuo to an oily solid residue. Extraction of this material with ethyl acetate (2 x 25 ml), washing with water, drying over anhydrous  $\text{Na}_2\text{SO}_4$ , filtering and concentration of the filtrate in vacuo gave a viscous yellow gum which contained minor impurities. The yield was essentially quantitative. NMR supported the structure and a molecular ion of M/Z 388 (M+H) was observed.

Step E: Preparation of 4-(1-Hydroxypropyl)-5-methylsulfonylthiophene-2-sulfonamide

To a stirred solution of 4-[1-(methoxyethoxymethoxy)propyl]-5-methylsulfonylthiophene-2-sulfonamide (8.0 g, 0.02 mol) in methanol (20 ml) was added a cold solution of concentrated sulfuric acid

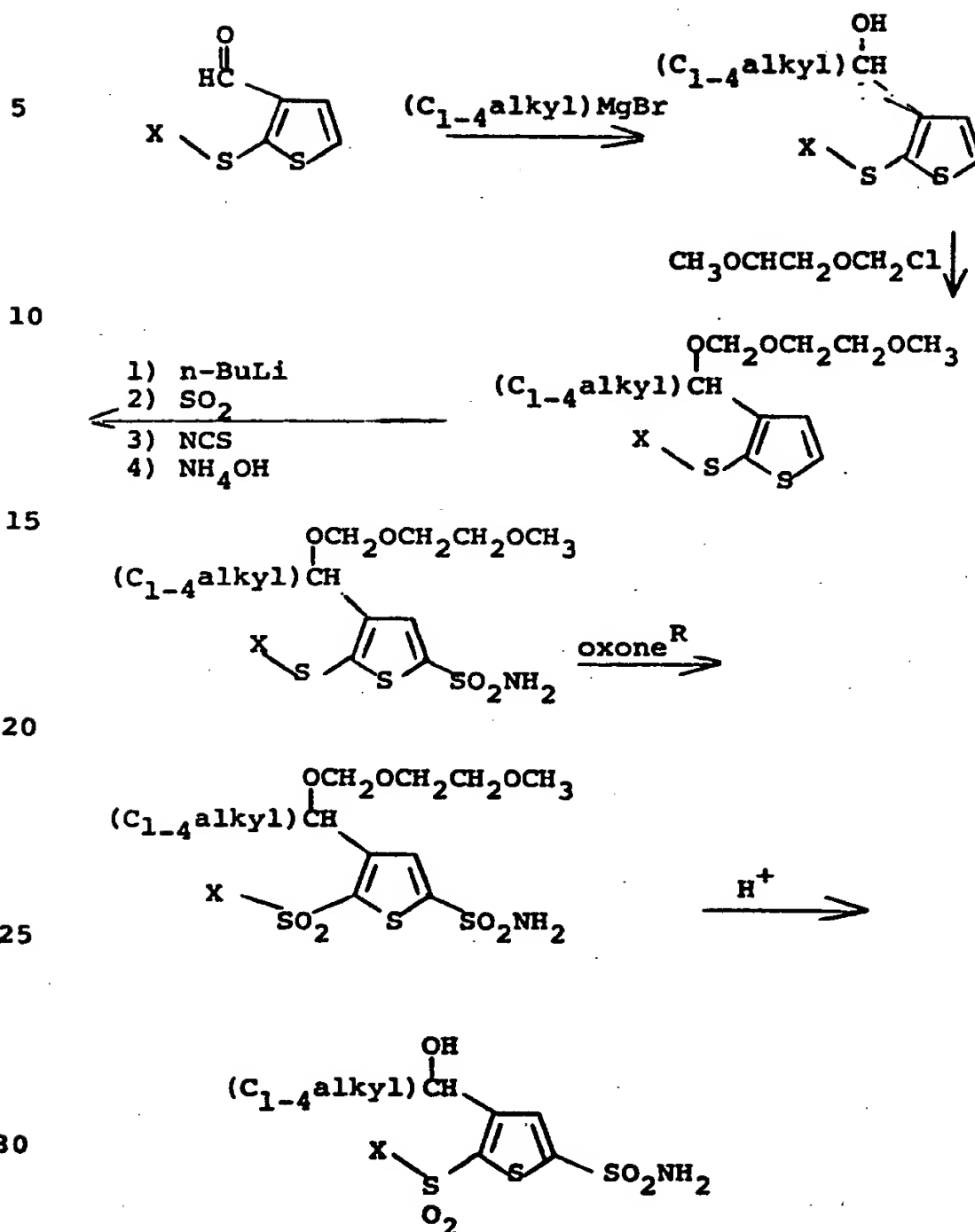
2151S/0245A

- 18 -

17324

(20 ml) in water (20 ml). The mixture was stirred at room temperature for 1 hour and the solution was basified with a slight excess of 40% NaOH and the suspension was filtered to remove precipitated salts. The filtrate was washed with ether and acidified with HCl. The acidified mixture was extracted with ethyl acetate (4 x 25 ml). The combined extracts were washed with saturated NaCl solution and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solution was filtered and concentrated in vacuo at room temperature to give a viscous yellow oil which was a mixture of five components. Chromatography on 300 g of silica gel eluting with 5% methanol/ $\text{CHCl}_3$  gave 3.0 g of a pure colorless oil. Trituration of the oil in n-butyl chloride gave a white solid (2.8 g) (45%). The product was recrystallized from 1,2-dichloroethane; m.p. 125.5-126.5°C.

Employing the procedures substantially as described in Example 1, but using as starting materials the alkylthiophenes and Grignard reagents described in Table I, there are produced the 4,5-disubstituted-thiophene-2-sulfonamides also described in Table I in accordance with the following reaction scheme:



2151S/0245A

- 20 -

17324

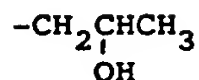
Table I

	<u>R</u>	$\text{OH}$ <u><math>(\text{C}_{1-4}\text{-alkyl})\text{-CH-}</math></u>	<u>m.p. (<math>^{\circ}\text{C}</math>)</u>
5	$-\text{CH}_3$	$\text{CH}_3\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	127-131
	$-\text{CH}_2\text{CH}_3$	$\text{CH}_3\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	122-124
10	$-\text{CH}_3$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	
15	$-\text{CH}_2\text{CH}_3$	$\text{CH}_3\text{CH}_2\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	
	$-\text{CH}_2\text{CH}_3$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	
20	$-\text{CH}_2\text{CH}_2\text{CH}_3$	$\text{CH}_3\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	
	$-\text{CH}_2\text{CH}_2\text{CH}_3$	$\text{CH}_3\text{CH}_2\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	
25	$-\text{CH}(\text{CH}_3)_2$	$\text{CH}_3\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	
30	$-\text{CH}(\text{CH}_3)_2$	$\text{CH}_3\text{CH}_2\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	
	$-\text{CH}_2\text{CH}_2\text{OH}$	$\text{CH}_3\text{-}\overset{\text{OH}}{\underset{ }{\text{CH}}}\text{-}$	

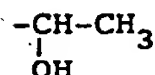
2151S/0245A

- 21 -

17324

Table I (Cont'd)

5

EXAMPLE 2

10 4-(2-Hydroxyethyl)-5-methylsulfonylthiophene-2-sulfon-  
amide

Step A: Preparation of 2-Bromo-3-(2-hydroxyethyl)-  
thiophene

To a stirred solution of 2-(3-thienyl)-  
15 ethanol (25.0 g, 0.195 mol) in carbon tetrachloride  
(250 ml) was added N-bromosuccinimide (34.7 g, 0.195  
mol) in several portions over a 15 minute period.  
The mixture was stirred at room temperature for one  
hour. The succinimide was removed by filtration and  
20 the filtrate was concentrated in vacuo at room  
temperature to give the product as a viscous amber  
oil (40.2 g) (99%). TLC indicated that the product  
was pure and mass spectral analysis showed a  
molecular ion at M/Z 206. NMR supported the  
25 structure.

Step B: Preparation of 2-Bromo-3-[2-(methoxyethoxy-  
methoxy)ethyl]thiophene

A solution of 2-bromo-3-(2-hydroxyethyl)-  
30 thiophene (40.0 g, 0.193 mol) in methylene chloride  
(200 ml) was cooled in ice and methoxyethoxymethyl  
chloride (41.9 g, 0.336 mol) was added with

stirring. After several minutes N,N-diisopropyl-ethylamine (44.3 g, 0.336 mol) was added and the solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was  
5 taken up in ether (150 ml) and water (75 ml). The ether layer was separated and was washed with saturated  $\text{NaHCO}_3$  solution and with water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated  
10 in vacuo at room temperature to give 52.1 g of an amber liquid. TLC indicated that the product was pure and NMR confirmed the structure. Field desorption mass spectral analysis gave a molecular ion of M/Z 294. The yield was 91%.

15 Step C: Preparation of 3-[2-(Methoxyethoxymethoxy)-ethyl]-2-methylthiophene

To a stirred solution of 2-bromo-3-[2-(methoxyethoxymethoxy)ethyl]thiophene (51.8 g, 0.175 mol) in anhydrous ether (125 ml) cooled to  $-70^\circ\text{C}$  was  
20 added n-butyl lithium (109.4 ml of a 1.6M solution in hexane, 0.175 mol) under a nitrogen atmosphere over a 1-1/2 hour period. A tan suspension resulted which was stirred for an additional 1 hour and then was diluted with dry THF (100 ml) and was passed under  
25 nitrogen into a stirred solution of dimethyldisulfide (18.8 g, 0.20 mol) in anhydrous ether (50 ml) at  $-15^\circ\text{C}$ . The resulting mixture was stirred at  $-15^\circ\text{C}$  for 1/2 hour and at reflux for 2 hours. The dark mixture was cooled to  $0^\circ\text{C}$  and water (100 ml) was  
30 added carefully. The organic layer was separated and washed with saturated NaCl solution, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in

vacuo at room temperature. The crude liquid (44.6 g) was distilled, the product being collected at 110-140°C at 0.7 mm to give 34.6 g of pure product. Yield 75%. NMR supported the structure.

5

Step D: Preparation of 4-[2-(Methoxyethoxymethoxy)-ethyl]-5-methylthiophene-2-sulfonamide

To a stirred solution of 4-[2-(methoxyethoxymethoxy)ethyl]-5-methylthiophene (34.4 g, 0.13 mol) in THF (250 ml) cooled to -40°C was added dropwise over 1/2 hour under nitrogen atmosphere n-butyl lithium (89.4 ml of a 1.6M solution in hexane, 0.143 mol). The resulting yellow solution was stirred at -40°C for an additional one hour.

15 Then anhydrous SO<sub>2</sub> was introduced over the surface of the solution for 1-1/2 hour at about -20°C. The solution was concentrated in vacuo at room temperature to a viscous yellow oil. The oil was dissolved in saturated NaHCO<sub>3</sub> solution (200 ml) and

20 N-chlorosuccinimide (24.4 g, 0.183 mol) was added portionwise over 1/2 hour at 5°C. Stirring was continued for an additional 2-1/2 hours at 0°C. The oil which had separated was extracted into chloroform, washed with water and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>.

25 Filtration and concentration of the filtrate in vacuo gave the sulfonyl chloride as an amber liquid. The liquid was dissolved in acetone (75 ml) and was added dropwise to concentrated NH<sub>4</sub>OH (150 ml) over 1/2 hour with ice bath cooling. The acetone was removed

30 in vacuo and the sulfonamide was extracted into chloroform. This solution was dried, filtered and concentrated in vacuo to give the crude sulfonamide



as an oil. The sulfonamide was extracted into 0.5N KOH solution (300 ml). The basic solution was washed with ether, acidified with 6N HCl, and extracted with ether. The ether extract was washed with water,  
5 dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo at room temperature to give 31.8 g (72%) of an amber oil. NMR supported the structure. Mass spectrum showed a molecular ion of M/Z 341.

10

Step E: Preparation of 4-[2-(Methoxyethoxymethoxy)-ethyl]-5-methylsulfonylthiophene-2-sulfonamide

The 4-[2-(methoxyethoxymethoxy)ethyl]-5-methylthiophene-2-sulfonamide (6.8 g, 0.02 mol)  
15 was dissolved in 50% aqueous ethanol (60 ml) and OXONE<sup>R</sup> (18.4 g, 0.03 mol) was added. The mixture was stirred at room temperature for 3 hours, then basified with  $\text{NaHCO}_3$ , filtered, and concentrated in vacuo at room temperature to an oily solid residue.  
20 The residue was extracted with 50/50 ethyl acetate/chloroform. The extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo to 6.6 g of colorless oil (88%). NMR supported the structure.

25

Step F: Preparation of 4-(2-Hydroxyethyl)-5-methylsulfonylthiophene-2-sulfonamide

The 4-[2-(methoxyethoxymethoxy)ethyl]-5-methylsulfonylthiophene-2-sulfonamide (6.6 g, 0.0177  
30 mol) was dissolved in methanol (25 ml) and was stirred at room temperature as cold 50% (v/v) sulfuric acid (40 ml) was added dropwise over 10

minutes. An additional quantity of methanol (25 ml) was added to dissolve the gum which separated and the solution was stirred for 1/2 hour. The solution was basified with sodium hydroxide and was washed with ether. The solution was acidified with HCl and was extracted with  $\text{CHCl}_3$  and then with ethyl acetate. The ethyl acetate extract was washed with saturated NaCl solution, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo at room temperature to give 4.1 g of crude oil which was chromatographed on silica gel (100 g) eluting with 5% methanol in chloroform. There was recovered 2.5 g of white solid which provided 1.5 g of analytically pure, material, m.p. 120-124°C.

### EXAMPLE 3

4-(1-Hydroxyethyl)-5-methylsulfinylthiophene--sulfonamide

Step A: Preparation of 4-[1-(Methoxyethoxymethoxy)-ethyl]-5-methylsulfinylthiophene-sulfonamide

To a stirred solution of 4-[1-(methoxyethoxymethoxy)ethyl]-5-methylthiothiophene-2-sulfonamide (6.8 g, 0.02 mol) in 50% aqueous ethanol (40 ml) was added sodium metaperiodate (4.8 g, 0.0224 mol). After several minutes solid began to separate. The mixture was stirred for 17 hours at room temperature. The suspension was filtered and the filtrate was concentrated to dryness in vacuo. The residual oily solid was chromatographed on silica gel (100 g) using 5% methanol in chloroform to give 6.68 g (94%) of pale yellow gum.

Step B: Preparation of 4-(1-Hydroxyethyl)-5-methyl-sulfinylthiophene-2-sulfonamide

To a stirred solution of 4-[1-(methoxyethoxymethoxy)ethyl]-5-methylsulfonylthiophene--  
5 sulfonamide (6.58 g, 0.0186 mol) in methanol (25 ml) was added dropwise over a 10 minute period a cold solution of 50% (by volume) sulfuric acid. The solution was stirred for an additional 20 minutes at room temperature. The reaction solution was basified  
10 with  $\text{NaHCO}_3$  with cooling and was concentrated to dryness in vacuo at 40°C bath temperature. The solid residue was extracted with hot ethyl acetate and with 20% methanol/ethyl acetate. Concentration of the extracts in vacuo gave 4.0 g of solid which was  
15 purified by chromatography on silica gel using 5% methanol in methylene chloride. There was obtained 3.0 g (60%) of product, m.p. 172-185°C.

EXAMPLE 4

20 4-(1-Methoxyethyl)-5-methylthiophene-2-sulfonamide

To a stirred solution of 4-[1-(methoxyethoxy-methoxy)ethyl]-5-methylthiophene-2-sulfonamide (6.8 g, 0.02 mol) in methanol (25 ml) was added dropwise 50% (by volume) cold sulfuric acid (50 ml)  
25 over a 10 minute period. The solution was stirred for an additional 1/2 hour at room temperature and the mixture was basified with  $\text{NaHCO}_3$  with cooling. The gum which separated was extracted into ethyl acetate. The aqueous layer was concentrated to  
30 dryness in vacuo and the solid residue was extracted with hot ethyl acetate. The ethyl acetate extracts were combined, dried over anhydrous  $\text{Na}_2\text{SO}_4$ ,

filtered and concentrated in vacuo to give an amber liquid which was purified by chromatography on silica gel (100 g) using ethyl acetate (40%)/hexane (60%). There was recovered 1.9 g (36%) of white solid, m.p. 86-94°C.

#### EXAMPLE 5

##### 4-(1-Hydroxyethyl)-5-methylthiophene-2-sulfonamide

To boron tribromide (40 ml of a 1.0M solution in methylene chloride) cooled under a nitrogen atmosphere to -50°C was added dropwise over 1/2 hour tetramethyl tin (7.15 g, 0.04 mol). The resulting solution was stirred for 1/2 hour at -50°C and then for 1/2 hour at 15°C. The solution was cooled to -78°C and 4-[1-(methoxyethoxymethoxy)ethyl]-5-methylthiophene-2-sulfonamide (3.41 g, 0.01 mol) in methylene chloride (15 ml) was added dropwise over 15 minutes. The mixture was stirred at -78°C for 3/4 hour and then poured into saturated NaHCO<sub>3</sub> solution. Some additional solid NaHCO<sub>3</sub> was added and the basic mixture was filtered. The filtrate was extracted with ethyl acetate (2 x 100 ml). The ethyl acetate solution was extracted with 0.5M KOH solution (2 x 100 ml). The KOH extracts were washed with ether and acidified with 6N HCl. The acidified mixture was extracted with ethyl acetate (2 x 50 ml). This extract was washed with saturated NaHCO<sub>3</sub>, water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo at ambient temperature. A pale amber oil was obtained (1.5 g). NMR confirmed the structure. After trituration in n-butyl chloride

the oil solidified. Recrystallization from 1,2-dichloroethane gave 0.54 g (21%) of white solid, m.p. 100-102°C.

5

EXAMPLE 64-(1-Acetamidoethyl)-5-methylsulfonylthiophene-2-sulfonamide

To acetonitrile (30 ml) was added concentrated sulfuric acid (2.94 g, 0.03 mol) followed by 4-(1-hydroxyethyl)-5-methylsulfonylthiophene-2-sulfonamide (2.85 g, 0.01 mol). The resulting solution was stirred at room temperature for 24 hours. Only about 1/2 of the alcohol had reacted so additional sulfuric acid (2.94 g, 0.03 mol) was added. After another 16 hours at room temperature the reaction was complete. The mixture was basified with excess  $\text{NaHCO}_3$ . Acetonitrile (100 ml) was added, the mixture was filtered and the acetonitrile was evaporated in vacuo. The residue was taken up in ethyl acetate, washed with saturated NaCl solution, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The solid obtained was recrystallized from water to give 1.1 g (34%) of yellow solid, m.p. 114-117°C. HPLC and TLC confirmed the purity and NMR confirmed the structure.

30

EXAMPLE 74-[1-(Ethylamino)ethyl]-5-methylsulfonylthiophene-2-sulfonamide

To a stirred refluxing solution of 4-(1-acetamidoethyl)-5-methylsulfonylthiophene-2-sulfonamide (2.52 g, 0.0077 mol) in dry tetrahydro-

furan (25 ml) under nitrogen atmosphere was added dropwise a solution of borane dimethylsulfide complex (2.3 ml, 0.023 mol) in THF (10 ml) over 1/2 hour. Reflux was continued for 1 hour. The solution was  
5 cooled in ice and acidified with 6N HCl (10 ml). The acidified solution was concentrated in vacuo. The residue was basified with saturated  $\text{NaHCO}_3$  solution and was extracted with ethyl acetate. The product was extracted into 3N HCl. This was again basified  
10 with saturated  $\text{NaHCO}_3$  solution, extracted with ethyl acetate, washed with saturated NaCl solution, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. A white solid was obtained (1.33 g) (55%), m.p. 162.5-165°C. Recrystallization  
15 from ethyl acetate gave 1.23 g of product, m.p. 164-165.5°C. HPLC and TLC confirmed the purity and NMR confirmed the structure.

#### EXAMPLE 8

20 5-(2-Hydroxyethylsulfonyl)-4-methylthiophene-2-sulfonamide

Step A: Preparation of 2-(2-Hydroxyethylthio)-3-methylthiophene

A mixture of 2-bromo-3-methylthiophene (53.1  
25 g, 0.30 mol), cuprous hydroxyethylmercaptide (46.4 g, 0.33 mol), pyridine (50 ml) and quinoline (200 ml) was stirred at reflux under nitrogen atmosphere for 4-1/2 hours. The mixture was cooled, poured into 6N HCl and ice (800 ml), and repeatedly extracted with  
30 ether. The ether extract was washed with water, saturated  $\text{NaHCO}_3$  solution and saturated NaCl solution and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The

solution was filtered and concentrated in vacuo to obtain a brown liquid (41.9 g). Chromatography on silica gel gave 36.6 g of a pale yellow oil, (70%). TLC indicated that the product was pure. The structure was supported by NMR and mass spectrometry showed a molecular ion of  $M/Z = 174$ .

Employing the procedures substantially as described in Example 1, Steps B, C, D and E there are produced in sequence starting with the product of Step A hereof:

- Step B: 2-[2-(methoxyethoxymethoxy)ethylthio]-3-methylthiophene, as an oil in 98% yield;
- Step C: 5-[2-(methoxyethoxymethoxy)ethylthio]-4-methylthiophene-2-sulfonamide, as an oil in 76% yield;
- Step D: 5-[2-(methoxyethoxymethoxy)ethylsulfonyl]-4-methylthiophene-2-sulfonamide, as an oil in quantitative yield; and
- Step E: 5-(2-hydroxyethylsulfonyl)-4-methylthiophene-2-sulfonamide, m.p. 144.5-148°C, in 29% yield.

#### EXAMPLE 9

##### 4,5-Bis(ethylthio)thiophene-2-sulfonamide

To a stirred solution of 2,3-bis(ethylthio)-thiophene (11.2 g, 0.055 mol) in dry tetrahydrofuran (100 ml) cooled to -78°C under nitrogen atmosphere was added dropwise over 1/2 hour 1.55M n-butyl lithium in hexane (39 ml, 0.0605 mol). The resulting amber solution was stirred at about -75°C for 1-1/2 hours. Anhydrous sulfur dioxide gas was introduced

over the surface of the solution over 1/2 hour at -75 to -20°C. The solution was stirred at -10 to -20°C for 1-1/2 hours. Concentration of the solution in vacuo gave the lithium salt as a pale yellow gum.

5 The gum was dissolved in saturated NaHCO<sub>3</sub> solution (100 ml) and N-chlorosuccinimide (11.2 g, 0.0825 mol) was added portionwise over 1/2 hour at ice bath temperature. After 3 hours at ice bath temperature the mixture was extracted with chloroform. The

10 extract was washed with water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to give the sulfonyl chloride as an amber oil. The sulfonyl chloride was dissolved in acetone (25 ml) and was added dropwise to concentrated NH<sub>4</sub>OH (100

15 ml) over 1/2 hour at ice bath temperature. After an additional hour at ice bath temperature the acetone was removed in vacuo and the oil which separated was extracted into ether. The product was extracted from the ether solution into 0.5N KOH solution. The KOH

20 extract was acidified with excess 6N HCl and the oil was re-extracted into ether, washed with saturated NaHCO<sub>3</sub> solution and water. It was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to a solid (8.1 g, 52%). Recrystallization

25 from n-butyl chloride gave 5.74 g of white solid, m.p. 82-84°C.

#### EXAMPLE 10

##### 4,5-Bis(ethylsulfonyl)thiophene-2-sulfonamide

30 The 4,5-bis(ethylthio)thiophene-2-sulfonamide (2.83 g, 0.01 mol) was dissolved in 50/50 ethanol/water (70 ml) and OXONE<sup>R</sup> (18.4 g, 0.03 mol) was



added. The mixture was stirred at room temperature for 72 hours. The suspension was filtered and the filtrate was basified with  $\text{NaHCO}_3$  and was concentrated in vacuo to dryness. Both the solid residue obtained and the solids filtered from the reaction suspension were extracted with methanol. The solid obtained upon evaporation of the methanol was taken up in ethyl acetate, washed with water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo at room temperature. White solid product was obtained (3.15 g) which contained some sulfoxide impurity. Recrystallizations from isopropanol and 50% aqueous methanol gave pure title compound (1.94 g, 56%), m.p.  $175.5\text{--}177^\circ\text{C}$ . HPLC and TLC confirmed the purity and NMR and mass spectrometry supported the structure.

#### EXAMPLE 11

##### 5-(1-Hydroxyethyl)-4-methylsulfonyl-2-sulfonamide

Step A: Preparation of 2-(1-Hydroxyethyl)-3-methylthiophene

To a stirred solution of methylmagnesium bromide (51.7 g, 0.15 mol) in dry ether (50 ml) under nitrogen atmosphere was added dropwise 3-methylthiophene-2-carboxaldehyde (15.8 g, 0.10 mol) in dry ether (25 ml) at about  $10^\circ\text{C}$ . The solution was stirred at room temperature for 2-3/4 hours, cooled and decomposed by cautiously adding  $\text{NH}_4\text{Cl}$  (16 g, 0.3 mol) in water (100 ml). The aqueous layer was separated and extracted with ether. The combined ether solution and extract were washed with saturated  $\text{NaCl}$  solution, dried over anhydrous  $\text{Na}_2\text{SO}_4$ ,

filtered and concentrated in vacuo at room temperature to a pale yellow oil which contained two components. Chromatography on silica gel gave pure product (13.5 g, 78%). NMR supported the structure.

5

Step B: Preparation of 2-[1-(Methoxyethoxymethoxy)-ethyl]-3-methylthiophene

To a stirred solution of 2-(1-hydroxyethyl)-3-methylthiophene (13.5 g, 0.077 mol) in dry methylene chloride (100 ml) was added methoxyethoxymethyl chloride (11.5 g, 0.092 mol) followed by N,N-diisopropylethylamine (12.1 g, 0.092 mol) with cooling. The solution was stirred at room temperature for 18 hours. Some starting material remained upon work up at this point. The material was recycled as above using 1/2 the above quantities of methoxyethoxymethyl chloride and N,N-diisopropylethyl amine. After 5 hours at room temperature the reaction was completed. The solution was washed with water, dilute HCl, saturated NaHCO<sub>3</sub> solution and again with water. Then it was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. Pure product was obtained as a yellow oil (17.6 g, 87%). TLC confirmed the purity and NMR and mass spectrometry (M/Z = 262) supported the structure.

Step C: Preparation of 5-[1-(Methoxyethoxymethoxy)-ethyl]-4-methylthiophene-2-sulfonamide

To a stirred solution of 2-[1-(methoxyethoxymethoxy)ethyl]-3-methylthiophene (17.6 g, 0.067 mol) in dry THF (100 ml) under nitrogen atmosphere and cooled to -78°C was added dropwise over 1 hour

1.55M n-butyl lithium (47.5 ml, 0.0737 mol) in hexane. The deep red solution was stirred at  $-78^{\circ}\text{C}$  for 1-1/2 hours. Then anhydrous sulfur dioxide gas was introduced over the surface of the solution at  $-78$  to  $-40^{\circ}\text{C}$  over 1 hour. Stirring at  $-40^{\circ}\text{C}$  was continued for 1-1/2 hours and the solution was concentrated in vacuo to give the lithium salt as a yellow oil. The lithium salt was dissolved in saturated  $\text{NaHCO}_3$  solution, (100 ml) and N-chlorosuccinimide (13.6 g, 0.10 mol) was added portionwise over 1/2 hour with ice bath cooling. After stirring for an additional 3 hours at ice bath temperature the mixture was extracted with chloroform. The extract was washed with water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo to obtain the sulfonyl chloride as a yellow oil. The sulfonyl chloride was taken up in acetone (50 ml) and was added dropwise to concentrated  $\text{NH}_4\text{OH}$  (100 ml) at ice bath temperature over 1/2 hour. After another 1-1/2 hours at ice bath temperature the acetone was removed in vacuo. The oil which separated was extracted into ether and then from the ether into 0.5N KOH. The KOH extract was acidified with excess 6N HCl and the product was re-extracted into ether. The ether extract was washed with saturated  $\text{NaHCO}_3$  solution, water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The product was obtained pure as an amber oil (14.6 g, 64%). NMR supported the structure and TLC confirmed the purity.

Step D: Preparation of 5-[1-(Methoxyethoxymethoxy)-ethyl]-4-methylsulfonylthiophene-2-sulfonamide

To a stirred solution of 5-[1-(methoxyethoxy-methoxy)ethyl]-4-methylthiothiophene-2-sulfonamide  
5 (5.98 g, 0.0175 mol) in 50/50 ethanol/water (70 ml) was added OXONE<sup>R</sup> (14.4 g, 0.0263 mol). The suspension was stirred at room temperature for 4-1/2 hours. The mixture was basified with excess NaHCO<sub>3</sub> and the entire mixture was concentrated to near  
10 dryness in vacuo. The residual moist solid was suspended in ethyl acetate and was filtered. The ethyl acetate extract was washed with water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated  
15 in vacuo to give a white solid, m.p. 93-102.5°C (6.4 g, 98%). NMR supported the structure and TLC confirmed that the material was pure.

Step E: Preparation of 5-(1-Hydroxyethyl)-4-methylsulfonylthiophene-2-sulfonamide

20 The 5-[1-(methoxyethoxymethoxy)ethyl]-4-methylsulfonylthiophene-2-sulfonamide (5.94 g, 0.0159 mol) was dissolved in 50/50 methanol/water (30 ml) with warming and concentrated sulfuric acid (15 ml) was added. The solution was cooled to ambient  
25 temperature and stirred for 1 hour. The methanol was removed in vacuo and the aqueous acid was diluted with water (50 ml). The product was extracted into ethyl acetate. The extract was washed with saturated NaHCO<sub>3</sub> solution, water, dried over anhydrous  
30 Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. A colorless oil was obtained which solidified to a

white solid. Several recrystallizations from water gave pure product (1.04 g, 23%), m.p. 121-127°C. NMR supported the structure and HPLC confirmed the purity.

5

EXAMPLE 135-Hydroxymethyl-4-methylsulfonylthiophene-2-sulfonamideStep A: Preparation of 2-Hydroxymethyl-3-methylthio-  
thiophene

To a stirred solution of 3-methylthiothio-  
10 phene-2-carboxaldehyde (15.8 g, 0.10 mol) in ethanol  
(150 ml) cooled to 10°C was added dropwise under  
nitrogen atmosphere a solution of sodium borohydride  
(3.78 g, 0.10 mol) in water (30 ml) and 1N KOH (5 ml)  
over 1/2 hour. The mixture was stirred at room  
15 temperature for 2 hours. The mixture was concentrated  
in vacuo at room temperature and the oily residue was  
taken up in chloroform (100 ml) and water (100 ml).  
The chloroform was separated and the aqueous layer  
was extracted with chloroform (50 ml). The combined  
20 chloroform extracts were washed with saturated NaCl,  
dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and  
concentrated in vacuo at room temperature to give a  
pale yellow liquid (14.2 g) which contained two  
components. Chromatography on silica gel gave 9.5 g  
25 (59%) of the title compound as a colorless oil. NMR  
supported the structure and mass spectral analysis by  
low resolution showed a molecular ion of M/Z = 160.

Employing the procedures substantially as  
30 described in Example 12, Steps B through E, there was  
produced in sequence starting with the product from  
Step A hereof:

- Step B: 2-(Methoxyethoxymethoxymethyl)-3-methylthio-  
thiophene as a yellow liquid in 95% yield;
- Step C: 5-(Methoxyethoxymethoxymethyl)-4-methylthio-  
thiophene-2-sulfonamide as an oil in 64%  
5 yield;
- Step D: 5-(Methoxyethoxymethoxymethyl)-4-methyl-  
sulfonylthiophene-2-sulfonamide in 95%  
yield, m.p. 104-107°C; and
- Step E: 5-Hydroxymethyl-4-methylsulfonylthiophene-2-  
10 sulfonamide in 72% yield, m.p. 175-177.5°C.

#### EXAMPLE 14

##### 5-Bromo-4-(1-hydroxyethyl)thiophene-2-sulfonamide

- Step A: Preparation of 2-Bromo-3-(1-hydroxyethyl)  
15 thiophene

To a stirred solution of 3-(1-hydroxyethyl)-  
thiophene (61.4g, 0.48 mol) in carbon tetrachloride  
(550 ml) was added N-bromosuccinimide (89.4g, 0.504  
mol) portionwise over 1 1/2 hours at 40°C. Stirring  
20 was continued for an additional 2 hours at ambient  
temperature. The reaction mixture was filtered and  
the filtrate was washed with water, saturated  
NaHCO<sub>3</sub> and again with water. The solution  
was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and  
25 concentrated in vacuo at room temperature. This  
procedure gave 95.5g (96%) of pale yellow oil. NMR  
supported the structure.

- Step B: Preparation of 2-Bromo-3-[1-(methoxy-  
30 ethoxymethoxy)ethyl]thiophene

A solution of 2-bromo-3-(1-hydroxyethyl)-  
thiophene (97.5g, 0.47 mol) in dry methylene chloride

(400 ml) was cooled in ice and N,N-diisopropyl-ethylamine (68.2g, 0.517 mol) was added followed by methoxyethoxymethyl chloride (64.4g, 0.517 mol). The solution was stirred at room temperature over night.

5 The dark solution was washed with water, 3N HCl, saturated  $\text{NaHCO}_3$  and finally with water. The solution was dried over anhydrous  $\text{Na}_2\text{SO}_4$  filtered and concentrated in vacuo at room temperature. A dark amber oil was obtained (123.1 g). The impure

10 product was distilled and the product was collected at 108-116°C at 0.7 mm Hg. to give 91.1g (66%) of colorless liquid. NMR supported the structure.

Step C: Preparation of 5-Bromo-4-[1-(methoxyethoxymethoxy)ethyl]thiophene-2-sulfonamide

15

To a stirred solution of dry diisopropylamine (12.6g, 0.125 mol) in dry THF (100 ml) cooled to -5°C under nitrogen atmosphere n-butyl lithium (66.7 ml of a 1.55 M hexane solution, 0.105 mol) was

20 added dropwise over 1/2 hour. The solution was stirred for 1-1/2 hours at -5°C. The resulting lithium diisopropylamide solution was added dropwise over 1 hour at below -70°C to a stirred solution of 2-bromo-3-[1-(methoxyethoxymethoxy)ethyl]thiophene

25 (29.5g, 0.10 mol) in dry THF (50 ml). The solution was stirred at -70°C for 1/2 hour and then at -70 to -50°C for 1/2 hour. Recooled to -70°C and anhydrous sulfur dioxide was introduced over the surface of the solution until the mixture became acidic.

30 Stirring was continued at -40 to -60°C for 1 hour and then the mixture was concentrated in vacuo at room temperature to give the lithio salt as a brown gum.

The gum was dissolved in water (200 ml) containing sodium acetate (18.0g, 0.22 mol) and the solution was cooled in an ice bath. Hydroxylamine-O-sulfonic acid (22.6g, 0.20 mol) was added. The mixture was  
5 slightly acidic so another portion of sodium acetate (18.0g, 0.22 mol) was added. The nearly neutral solution was stirred at room temperature over night. The mixture was extracted with chloroform (200 ml in 3 portions) and the sulfonamide was extracted into  
10 0.5N KOH (200 ml). The KOH extract was washed with ether, acidified with excess 6N HCl and re-extracted into ether (300 ml). The ether extract was washed with saturated  $\text{NaHCO}_3$  and water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated  
15 in vacuo to give 26.0g (69%) of a viscous oil which solidified to a waxy solid. NMR supported the structure.

Step D: Preparation of 5-Bromo-4-(1-hydroxyethyl)-  
20 thiophene-2-sulfonamide  
5-Bromo-4-[1-(methoxyethoxymethoxy)ethyl]-thiophene-2-sulfonamide (5.3g, 0.014 mol) was dissolved in methanol (25 ml) and water (25 ml) was added. Some oil separated. To this stirred mixture  
25 was added sulfuric acid (25 ml) dropwise with cooling over 20 minutes. The resulting solution was stirred at room temperature over night. The methanol was removed in vacuo and the residual suspension was diluted with two volumes of water. The product was  
30 extracted into ethyl acetate. The extract was washed with saturated  $\text{NaHCO}_3$ , water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. This



gave 4.0g of a viscous amber oil. The crude oil was chromatographed on silica gel (150 ml) eluting with 5% methanol/chloroform to give 1.96g of colorless oil which showed a single spot by TLC. Trituration of the oil in n-butyl chloride gave a white solid (1.69g, 49%), m.p. 126-128.5°C. NMR supported the structure.

#### EXAMPLE 15

10 4-(1-(ethylamino)ethyl)-5-ethylsulfonylthiophene-2-sulfonamide

Step A: Preparation of 4-(1-Acetamidoethyl)-5-ethylsulfonylthiophene-2-sulfonamide

To acetonitrile (40 ml) was added concentrated sulfuric acid (8.1g, 0.0828 mol). Then 5-ethylsulfonyl-4-(1-hydroxyethyl)thiophene-2-sulfonamide (4.14g, 0.0138 mol) was added and the solution was stirred at room temperature until no starting material remained (48 hours). The solution was neutralized by adding solid NaHCO<sub>3</sub> along with water (5 ml). The mixture was filtered and the solids were washed with acetonitrile. The filtrate and washings were concentrated in vacuo to an oil. This residual oil was taken up in ethyl acetate (125 ml). The extract was washed with saturated NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo at room temperature, to give 2.74g (58%) of white solid which was a single product by TLC, m.p. 213-220°C. NMR supported the structure.

Step B: Preparation of 4-[1-(Ethylamino)ethyl]-5-ethylsulfonylthiophene-2-sulfonamide

To a stirred, refluxing suspension of 4-(1-acetamidoethyl)-5-ethylsulfonylthiophene-2-sulfon-  
5 amide (2.61g, 0.0077 mol) in dry tetrahydrofuran under nitrogen atmosphere was added dropwise over 1/2 hour a solution of dimethylsulfide borane complex (2.3 ml of a 10 M solution, 0.023 mol) in dry THF (10 ml). The cloudy solution which formed was stirred at  
10 reflux for 1-1/2 hours. The mixture was cooled in ice and acidified by the dropwise addition of 6N HCl (10 ml), and concentrated in vacuo at room temperature. The moist solid residue was basified with saturated  $\text{NaHCO}_3$  and was extracted with ethyl  
15 acetate (4 x 50 ml). The amino product was extracted into 3N HCl (4 x 25 ml). The combined HCl extracts were neutralized with  $\text{NaHCO}_3$  and extracted with ethyl acetate (4 x 50 ml). The ethyl acetate extract was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and  
20 concentrated in vacuo at room temperature. A colorless oil was obtained which solidified to a white solid upon trituration in ethyl acetate. The crude yield was 1.99g or 80%. The solid after recrystallization from ethyl acetate had m.p.  
25 135-137.5°C. NMR supported the structure and HPLC confirmed the purity.

2151S/0245A

- 42 -

17324

EXAMPLE 16

4-(1-Hydroxyethyl)-5-ethyl-  
sulfonylthiophene-2-  
sulfonamide

1 mg.      15 mg.

5

Monobasic sodium phosphate  $.2H_2O$       9.38 mg.      6.10 mg.

Dibasic sodium phosphate  $.12H_2O$       28.48 mg.      16.80 mg.

10 Benzalkonium chloride      0.10 mg.      0.10 mg.

Water for injection q.s. ad.      1.0 ml.      1.0 ml.

15      The title Compound, phosphate buffer salts,  
and benzalkonium chloride are added to and dissolved  
in water. The pH of the composition is adjusted to  
6.8 and diluted to volume. The composition is  
rendered sterile by ionizing radiation.

20

EXAMPLE 17

4-(1-Hydroxypropyl)-5-ethyl-  
sulfonylthiophene-2-sulfonamide

5 mg.

25 petrolatum q.s. ad.

1 gram

30

The title compound and the petrolatum are  
aseptically combined.

30

EXAMPLE 18

4-(1-Hydroxyethyl)-5-ethylsulfonyl-  
thiophene-2-sulfonamide

1 mg.

5 Hydroxypropylcellulose q.s.

12 mg.

Ophthalmic inserts are manufactured from compression molded films which are prepared on a Carver Press by subjecting the powdered mixture of the above ingredients to a compressional force of 12,000 lbs. (gauge) at 300°F for one to four minutes. The film is cooled under pressure by having cold water circulate in the platen. Ophthalmic inserts are then individually cut from the film with a rod-shaped punch. Each insert is placed into a vial, which is then placed in a humidity cabinet (88% R.H. at 30°C) for two to four days. After removal from the humidity cabinet, the vials are stopped and then capped. The vials containing the hydrate insert are then autoclaved at 250°F for 1/2 hour.

EXAMPLE 19

4-(2-Hydroxyethyl)-5-methylsulfonyl-  
thiophene-2-sulfonamide

1 mg.

25

Hydroxypropyl cellulose q.s. ad.

12 mg.

Ophthalmic inserts are manufactured from a solvent cast film prepared by making a viscous solution of the powdered ingredients listed above using methanol as the solvent. The solution is

placed on a Teflon plate and allowed to dry at ambient conditions. After drying, the film is placed in an 88% R. H. cabinet until it is pliable. Appropriately sized inserts are cut from the film.

5

EXAMPLE 20

4-[1-(Ethylamino)ethyl]-5-methyl-  
sulfonylthiophene-2-sulfonamide 1 mg.

10

Hydroxypropylmethyl cellulose q.s. ad. 12 mg.

Ophthalmic inserts are manufactured from a solvent cast film which is prepared by making a viscous solution of the powdered blend of the above ingredients using a methanol/water solvent system (10 ml. methanol is added to 2.5 g. of the powdered blend, to which 11 ml. of water (in three divided portions) is added. The solution is placed on a Teflon plate and allowed to dry at ambient conditions. After drying, the film is placed in an 88% R. H. cabinet until it is pliable. Appropriately sized inserts are then cut from the film.

25

EXAMPLE 21

5-(2-Hydroxyethylsulfonyl)-4-methyl-  
thiophene-2-sulfonamide 1 mg.

30

Hydroxypropylmethyl cellulose q.s. ad. 12 mg.

Ophthalmic inserts are manufactured from compression molded films which are prepared on a

Carver Press by subjecting the powdered mixture of the above ingredients to a compressional force of 12,000 lbs. (gauge) at 350°F for one minute. The film is cooled under pressure by having cold water circulate in the platen. Ophthalmic inserts are then individually cut from the film with a punch. Each insert is placed into a vial, which is then placed in a humidity cabinet (88% R. H. at 30°C) for two to four days. After removal from the humidity cabinet, the vials are stopped and then capped. The vials containing the hydrated insert are then autoclaved at 250°F for one-half hour.

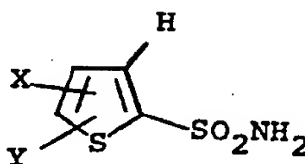
It is highly preferred that the solid inserts of this invention are available for use by the patient in a pathogen free condition. Thus, it is preferred to sterilize the inserts and to insure against recontamination, the sterilization is preferably conducted after packaging. The best mode of sterilizing is to employ ionizing radiation including radiation emanating from Cobalt 60 or high energy electron beams.

25

30

WHAT IS CLAIMED IS:

1. A compound of structural formula:



10 wherein:

- X is
- 1) -CN,
  - 2) halo,
  - 3) R wherein R is C<sub>1-5</sub> alkyl, either straight or branched chain and either unsubstituted or substituted with one or more of:

i) -OH

ii)  $\begin{array}{c} R^1 \\ \diagup \\ -N \\ \diagdown \\ R^2 \end{array}$  wherein R<sup>1</sup> and R<sup>2</sup>

are independently hydrogen, C<sub>1-5</sub> alkyl or C<sub>2-5</sub> alkanoyl,

iii) aryl, either unsubstituted or substituted with one or more of

-OH, or C<sub>1-3</sub> alkyl, or

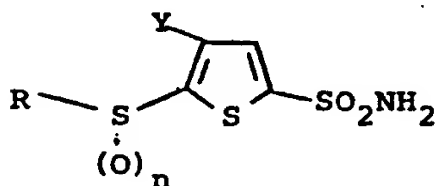
iv) a 6-membered nitrogen-containing heteroaryl;

4)  $\begin{array}{c} O \\ || \\ R-C- \end{array}$ ; or

5)  $\begin{array}{c} (O)_n \\ | \\ R-S- \end{array}$  wherein n is 0, 1 or 2.

- Y is
- 1)  $C_{1-5}$  alkyl, either straight chain, branched chain or cyclic, and either unsubstituted or substituted with
    - a) hydroxy,
    - 5 b)  $C_{1-3}$  alkoxy,
    - c) methoxyethoxymethoxy,
    - d) amino,
    - e)  $C_{1-5}$  alkylamino,
    - f)  $C_{2-5}$  alkanoylamino,
    - 10 g) aryl, either unsubstituted or substituted with one or more of -OH or  $C_{1-3}$  alkyl, or
    - h) a 6-membered nitrogen containing heteroaryl group;
  - 15 2)  $-S-(C_{1-5} \text{ alkyl})$ , where the alkyl is  $(O)_n$  either straight, branched or cyclic, and either unsubstituted or substituted with items a) through h) as defined
  - 20 above; and
  - 3) halo;
- with the proviso that X and Y are not both halo.

25 2. The compound of Claim 1 of structural formula:





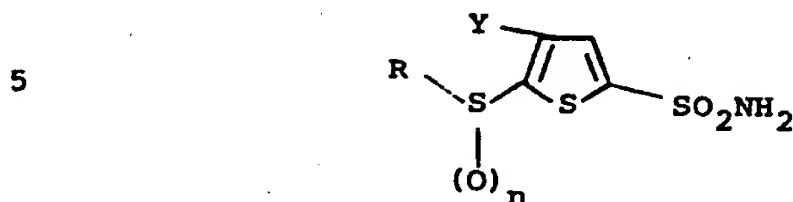
3. The compound of Claim 2 wherein R and Y are independently C<sub>1-5</sub> alkyl or substituted C<sub>1-5</sub> alkyl.

5           4. The compound of Claim 3 wherein R is C<sub>1-5</sub> alkyl, hydroxy-C<sub>1-5</sub> alkyl or mono- or di-(C<sub>1-5</sub> alkyl)amino-C<sub>1-5</sub> alkyl, and n is 0 or 2.

5. The compound of Claim 1 which is:  
10   4-(1-hydroxyethyl)-5-methylsulfonylthiophene-2-sulfonamide;  
     4-(1-hydroxypropyl)-5-methylsulfonylthiophene-2-sulfonamide;  
     4-(1-hydroxyethyl)-5-ethylsulfonylthiophene-2-sulfonamide;  
15       amide;  
     4-(2-hydroxyethyl)-5-methylsulfonylthiophene-2-sulfonamide;  
     4-hydroxymethyl-5-ethylsulfonylthiophene-2-sulfonamide;  
     5-(2-hydroxyethylsulfonyl)-4-methylthiophene-2-sulfonamide;  
20       amide; and  
     4,5-bis(ethylsulfonyl)thiophene-2-sulfonamide.

6. An ophthalmological composition for the treatment of elevated intraocular pressure which  
25   comprises an ophthalmologically acceptable carrier and an effective intraocular pressure lowering amount of a compound as defined in Claim 1.

7. The composition of Claim 6 wherein the compound has structural formula.



8. The composition of Claim 7 wherein R and  
10 Y are independently  $\text{C}_{1-5}$  alkyl, or substituted  
 $\text{C}_{1-5}$  alkyl.

9. The composition of Claim 8, wherein R is  
 $\text{C}_{1-5}$  alkyl, hydroxy- $\text{C}_{1-5}$  alkyl or mono- or  
15 di-( $\text{C}_{1-5}$  alkyl)amino- $\text{C}_{1-5}$  alkyl, and n is 0 or 2.

10. The composition of Claim 7 wherein the compound is:

- 20 4-(1-hydroxyethyl)-5-methylsulfonylthiophene-2-sulfonamide;  
4-(1-hydroxypropyl)-5-methylsulfonylthiophene-2-sulfonamide;  
4-(1-hydroxyethyl)-5-ethylsulfonylthiophene-2-sulfonamide;  
25 4-(2-hydroxyethyl)-5-methylsulfonylthiophene-2-sulfonamide;  
4-hydroxymethyl-5-ethylsulfonylthiophene-2-sulfonamide;  
5-(2-hydroxyethylsulfonyl)-4-methylthiophene-2-sulfonamide; and  
30 4,5-bis(ethylsulfonyl)thiophene-2-sulfonamide.



European Patent  
Office

# EUROPEAN SEARCH REPORT

0228237

Appl. cat. on number

EP 86 30 9815

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
Y	GB-A-1 459 571 (PFIZER) * Claims *	1, 2, 6, 7	C 07 D 333/34 A 61 K 31/38
Y	GB-A-1 468 111 (PFIZER) * Claims *	1, 6	
Y	EP-A-0 042 731 (Claims)	1	
Y	EP-A-0 130 109 (MERCK) * Claims *	1, 2, 6, 7	
P, Y	EP-A-0 182 691 (MERCK) * Claims *	1, 2, 6, 7	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 333/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 20-03-1987	Examiner CHOULY J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	